

Eliminating remnant CA 19-9 half-life-dependent antigen: An innovative approach for a more accurate interpretation of tumour marker follow-up

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Abstract

Objectives: Tumour markers provide insights into the course of disease and response to therapy in carcinoma patients, allowing physicians to determine changes in marker levels during disease. We aimed to evaluate the value of newly produced CA 19-9 levels in determining the response to treatment and prognosis in patients with pancreatic adenocarcinoma.

Methods: In a patient with pancreatic carcinoma, remnant CA 19-9 levels were determined by calculating the amount of biological decay of half-life-dependent CA 19-9. The amount of newly produced CA 19-9 was determined by subtracting the remnant CA 19-9 concentration from the actual CA 19-9 concentration.

Results: The calculated levels of newly produced and remnant CA 19-9 varied according to the sampling frequency and biological half-life of the tumor marker. Throughout the disease, the shape and gradient of the curve for the level of newly produced CA 19-9 were shifted compared with those for the actual measured serum levels.

Conclusions: The level of newly produced CA 19-9 significantly differs from the actual measured serum levels. The amount of newly produced CA 19-9 provides a more realistic and accurate indication of the effects of treatment and prognosis throughout the course of disease.

Keywords

Pancreatic carcinoma; Follow-up; Remnant CA 19-9; CA 19-9 half-life; Tumor marker.

Introduction

Tumour markers provide insight into the course of disease, response to therapy, and prognosis of patients with pancreatic adenocarcinoma, allowing physicians to determine marker level changes during disease. CA 19-9 (carbohydrate antigen sialyl Lewis A) is currently the only tumor marker approved by the United States Food and Drug Administration [1] for pancreatic cancer and is also considered to be the most clinically useful biomarker for the early detection and surveillance of pancreatic cancer by the National Comprehensive Cancer Network [2]. Therefore, this tumor marker is used as a reliable indicator of response to chemotherapy, time to tumor development, prognosis, and overall survival. It is currently the most extensively studied and, thus, the gold standard biomarker for the diagnosis of pancreatic cancer in symptomatic patients [3-8]. Elevated serum CA 19-9 levels are suggestive of pancreatic cancer recurrence, whereas decreased levels may predict favorable outcomes in patients treated for advanced pancreatic carcinoma [9-13]. According to the current guidelines of the American Society of Clinical Oncology, routine testing for this biomarker alone is not recommended for monitoring response to treatment [14,15]. Its predictive role is unclear, and there is no agreement about the extent of clinically relevant decrease or increase in CA 19-9 levels [16,17]. Serum CA 19-9 levels are usually measured during surveillance to detect cancer progression. These measurements are cost-effective and often show a lead time of several weeks to imaging in determining cancer prognosis [10,18]. Conventional follow-up curves generally present the biomarker levels determined in serial blood samples using commercially available test kits from several providers. The test result is used as a reference for interpreting the patient's status and response to therapy. However, the values determined from the samples represent a mixed concentration of both remnant biomarkers in the foregoing samples that have not been entirely eliminated from the blood and new incoming biomarkers delivered from the tumor, resulting in an inaccurate representation of the determined tumor marker concentrations.

Additionally, the remnant concentrations are correlated with their biological half-lives and the frequency of blood draws. Hence, the not-yet decayed CA 19-9 glycoproteins must be considered when measuring CA 19-9 levels in blood samples.

Tumor markers can be released by active secretion, passive shedding from the vital cell surface, or after a necrotic process due to therapy. Necrosis, especially after therapy, can lead to significantly increased CA 19-9 concentrations from the tissue, resulting in an overload in receiving blood vessels. This could mask the possibly reduced, effectively delivered marker concentration as a result of therapy. Therefore, in conventional follow-up, the measured CA 19-9 levels may include contributions that are inconsistent with the actual newly produced biomarker levels. Such false values can lead to diagnostic misinterpretation and fatal mistakes in prognosis and therapy. The amount of newly produced CA 19-9 (NP) can be derived from the actual measured levels in blood draws by a mathematical method. The resulting value represents the amount of NP at each blood draw and is thought to be a crucial indicator of response, therapy control, and prognosis.

The aim of our study was to introduce and propose a more distinct analysis of the specific tumor

marker release during follow-up throughout therapy. We determined the effective, present CA 19-9 influx concentrations using calculations derived from the results of serial sampling with respect to the biological half-life of CA 19-9 in the peripheral blood. This innovative approach may lead to the emergence of a more accurate marker level follow-up curve, enabling a more precise interpretation of treatment effects and prognosis by revealing the concentration of NP.

We used the clinical data of a patient with pancreatic carcinoma to provide a theoretical base for understanding the influence of tumor marker biological half-life as well as the frequency and timing of blood draws. Herein, we describe a new approach for constructing a more reliable tumor marker follow-up curve of a necrosis based tumor marker to improve prognostic judgment during follow-up. We performed the calculation using an in-house model with assumed constraints.

Materials and Methods

Our study refers to the data of an individual case report. Estimation of the treatment result was performed by calculating the NP concentration without prior inherited “waste” concentrations. According to the literature [7,18-22] the biological half-life of CA 19-9 was assumed to be 4-8 days to calculate its biological decay. The amount of decay and NP levels were computed from the resulting values of each CA 19-9 probe by subtracting the calculated amount of biological decay of the previously determined CA 19-9 serum levels from the actual determined CA 19-9 concentrations.

Serum CA 19-9 levels were determined using blood sample from a 71-year-old male patient with pancreatic adenocarcinoma (stage IV; Eastern Cooperative Oncology Group Performance Status of 1; no cholestasis; levels of bilirubin and liver enzymes alanine transaminase and aspartate transaminase within normal range) treated with 12 cycles of FOLFIRINOX [23,24] every 2 weeks. All data were acquired using electrochemical luminescence immunoassay with Elecsys CA 19-9 reagents and cobas e 801 devices (Roche Diagnostics, Mannheim, Germany). In addition to blood draws and medical check-ups at every cycle, surveillance Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) were performed every 2 months.

Assuming monophasic decay, the biological half-life was calculated using the following formula:

$$SL(t) = SL(t_0) e^{-(\ln 2/t(1/2)) \cdot t}$$

where $SL(t)$ represents the calculated serum level at time t , $SL(t_0)$ is the measured serum level at the time of blood draw, and $t(1/2)$ represents the half-life for biological decay [25].

Biphasic decay is cited for CA 19-9 in lung cancer, with an average biological half-life of 0.5 days in the first phase and 4.3 days in the second phase [26]. If blood is drawn weekly, the calculated amount of remnant CA 19-9 in the first phase is only 0.6% and thus, can be disregarded. Therefore, monophasic biological decay is assumed for simplicity.

With each blood draw, the amount of monophasic decay load (DL) is calculated by the sum of the

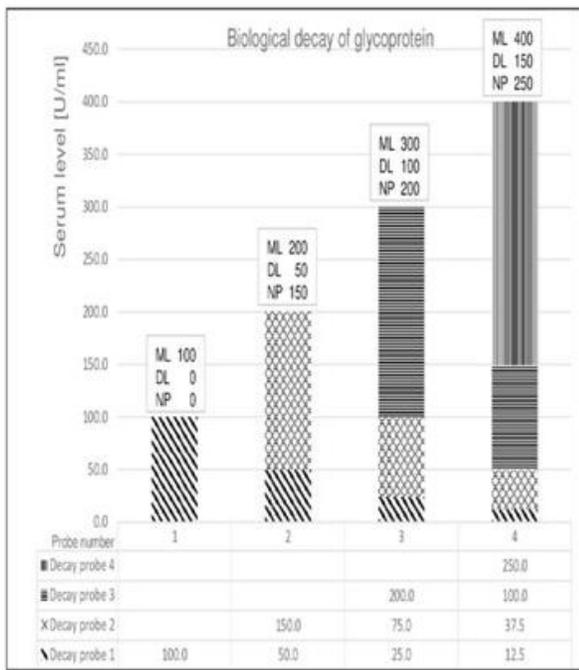


Figure 1: Consecutive fictive blood sample throughout the biological half-life of a glycoprotein (7 days). Probes 2-4 contain an amount of not-yet decayed glycoprotein from earlier samples. The amounts in U/ml for measured level (ML), calculated decay load (DL), and calculated newly produced CA 19-9 (NP) are shown in the corresponding boxes. The DL is the sum of decayed glycoproteins calculated at the time of the actual blood sample. For probe 4, $DL = 12.5 \text{ U/ml} + 37.5 \text{ U/ml} + 100 \text{ U/ml} = 150 \text{ U/ml}$. The NP is derived by computing the actual ML minus DL. In the case of probe 4, the $NP = 400 \text{ U/ml} - 150 \text{ U/ml} = 250 \text{ U/ml}$.

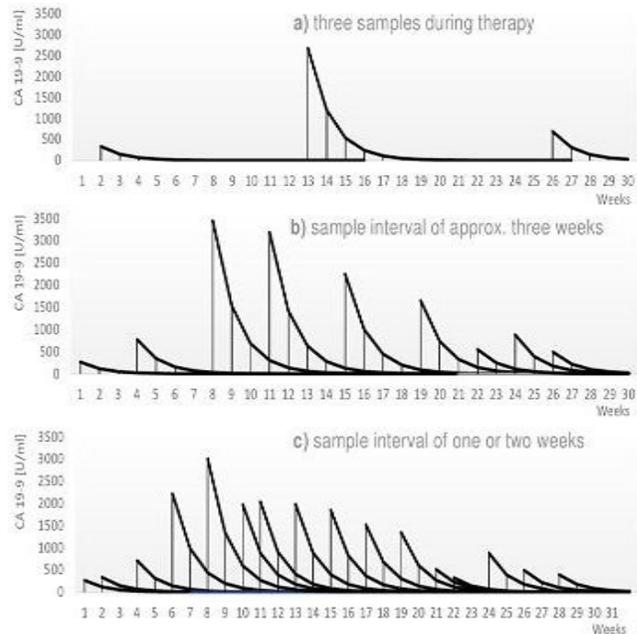


Figure 2: Calculated amounts of newly produced and biologically decayed CA 19-9 with an assumed biological half-life of 6 days during chemotherapy (first cycle at week 3, last cycle at week 26). The vertical lines are drawn to guide the eyes. With decreasing time between samples, the superposition of decay amounts increases. a) Samples at the beginning, middle, and end of therapy show no superposition of decay amounts. b) Samples taken at intervals of approximately 3 weeks show a slight superposition of decay amounts. c) Samples taken at intervals of 1 or 2 weeks show a distinct superposition of decay amounts.

contributions from the initial measurements at time $t(0)$ until the current measurement at time t . As an example, in Figure 1, if four assumed values of fictive blood samples are taken in periods of the biological half-life of CA 19-9, even the fourth blood sample will contain an amount of not-yet decayed CA 19-9 from the first sample. From Figure 1, the DL at the fourth sample is $12.5 \text{ U/ml} + 37.5 \text{ U/ml} + 100 \text{ U/ml} = 150 \text{ U/ml}$. The amount of NP can be derived by computing the actual measured level in the serum (ML) minus the DL. From Figure 1, the amount of NP is $400 \text{ U/ml} - 150 \text{ U/ml} = 250 \text{ U/ml}$.

Results

Using an assumed biological half-life of 6 days for CA 19-9, the calculated levels of NP showed detectable amounts of biological decay in blood tests for several weeks (Figure 2a-c), which were superposed by the decay from previous probes depending on the sample intervals. For example, when only a few samples were taken (i.e., in the beginning, middle, and end of therapy), the decay levels were not superposed by the new levels (Figure 2a). When samples were taken at intervals of approximately 3 weeks, a slight superposition of decay levels was observed (Figure 2b). Finally, when samples were taken at intervals of 1 or 2 weeks, a distinct superposition of decay amounts was visible (Figure 2c).

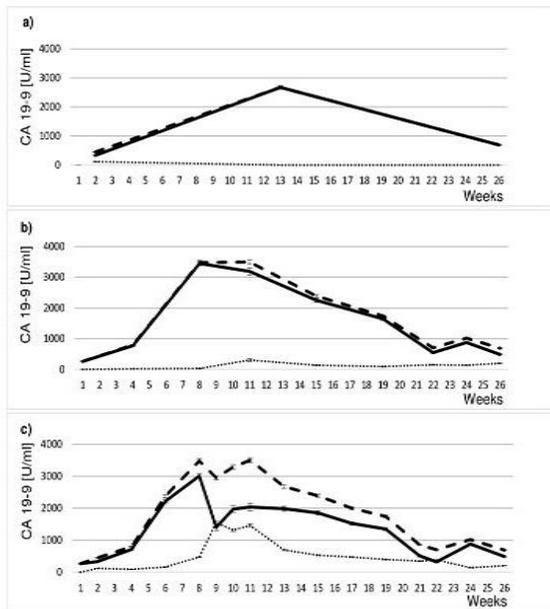


Figure 3: Measured levels in the serum (dashed line), calculated newly produced (solid line), and calculated biologically decayed (dotted line) CA 19-9 with an assumed biological half-life of 6 days during chemotherapy (first cycle at week 3, last cycle at week 26).
 a) Samples at the beginning, middle, and end of therapy.
 b) Samples taken at intervals of approximately 3 weeks.
 c) Samples taken at intervals of 1 or 2 weeks. The inaccuracy of measured and computed values is represented as percentages by the error bar.

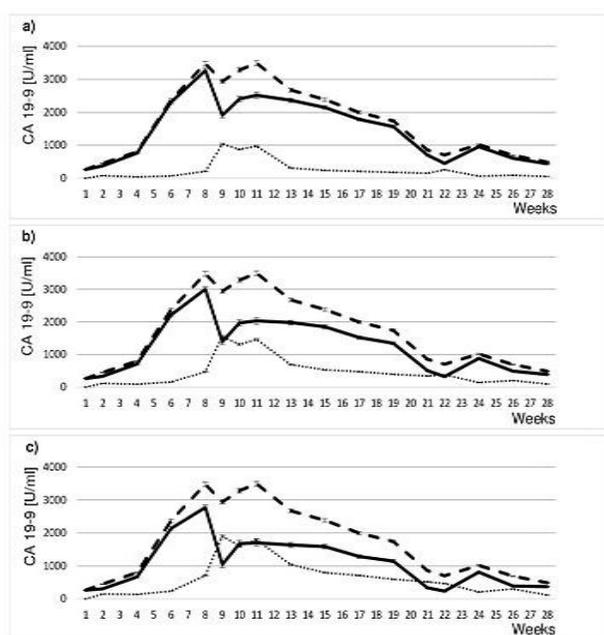


Figure 4: Measured levels in the serum (dashed line), calculated newly produced (solid line), and biologically decayed (dotted line) CA 19-9 with an assumed biological half-life of 4 (a), 6 (b), and 8 (c) days during chemotherapy (first cycle at week 3, last cycle at week 26). The inaccuracy of measured and computed values is represented as percentages by the error bar.

Using a biological half-life of 6 days, the ML, DL, and NP were plotted against time (Figure 3a-c). When only a few samples were taken (i.e., in the beginning, middle, and end of therapy), no remarkable difference between the ML and NP values was observed, as the amount of biological decay from the first and second samples was zero (Figure 3a). When samples were taken at intervals of approximately 3 weeks, a slight difference between the ML and NP was observed owing to the superposition of small amounts of decay (Figure 3b). In contrast, when samples were taken at intervals of 1 or 2 weeks, a distinct difference between the ML and NP was observed owing to a significant superposition of decay amounts (Figure 3c).

To analyze the effect of varying the assumed biological half-life, the ML, NP, and DL were plotted against time using a half-life of 4, 6, and 8 days (Figure 4a-c). The decrease in the NP significantly differed from those of the ML values. As the assumed biological half-life was increased, the difference between the ML and NP values became more pronounced.

Discussion

To the best of our knowledge, no previous study has evaluated biological decay in measurements of serum CA 19-9 levels. The current study, based on an individual case, provides several key takeaways. First, the level of newly produced CA 19-9 shows detectable biological decay for several weeks in serial blood sampling. Second, when blood samples are taken at long intervals compared to the biological half-life of the

tumor marker, rapid changes in serum levels between the tests will not be visible, resulting in a misunderstanding of the changes in tumor activity. However, the calculation of the actual continuous decay and new production is the same because the comparison is made based on measurements taken with a long time interval between them.

Thus, the amount of decay from the first probe would have already diminished by the time of the next blood sample, and no information regarding the serum levels between these two time points exists.

We also found that when the time between samples approaches the assumed biological half-life of the tumor marker, differences between the measured serum levels and corresponding calculated amounts of NP can be observed. Moreover, when samples are taken at an interval of approximately 3 weeks (assumed CA 19-9 biological half-life of 6 days), a slight difference between the ML and their corresponding calculated levels of new production is observed owing to the superposition of small decay amounts. When samples are taken in intervals of 1 or 2 weeks (assumed CA 19-9 biological half-life of 6 days), a distinct difference between values is observed owing to the superposition of decay amounts. This difference varies according to the biological half-lives of 4, 6, and 8 days because the DL increases with half-life. Thus, increasing the assumed biological half-life leads to an increase in the difference between measured levels and the corresponding calculated amounts of new production. Additionally, in these conditions with increasing MLs at the beginning of the time course, the influx curve of NP initially follows that of MLs. At the peak around week 8, the amount of NP is smaller than the ML. With decreasing MLs in the time course directly behind the peak, the shape of the curve for NP becomes sharper and is shifted downwards, with a rapid decline of NP levels compared with the measured CA 19-9 levels (Figure 4). This is significant as the decline in the slope is considered to be an important indicator of therapy response [12,18,27-34]. A pronounced peak can be interpreted as a consequence of tumor necrosis as a toxic effect of chemotherapy [35,38]. With decreasing amounts of measured and newly produced levels toward the end of the time course, the difference between the ML and NP becomes smaller, as the contribution of DL is less pronounced with smaller amounts of measured CA 19-9 levels.

Overall, our study demonstrates that by subtracting the half-life-dependent, remnant marker concentration of the prior samples from the present CA 19-9 concentration, only an estimate of the NP concentration can be made. An interval of 1 or 2 weeks between samples can improve the prognostic judgment during follow-up visits. The kinetics (shape and gradient) of the new CA 19-9 curve enables clinicians to determine the tumor's response to chemotherapy.

CA 19-9 in pancreatic cancer tissue is mostly found on the luminal cell surface and in the luminal content of the glandular structure [39]. In tumor-free pancreatic tissue adjacent to the tumor, CA 19-9 is detected almost exclusively in the cells of large- and medium-sized ducts [39]. Moreover, cancer cells, especially those of adenocarcinoma, express aberrant forms or amounts of mucins [40]. The mucins MUC1, MUC5AC, and MUC16 are major cancer-associated carriers of the CA 19-9 antigen in the blood [41]. Because CA 19-9-bearing mucins are pancreatic secretion exocrine products, they are thought to accumulate in the blood of patients with pancreatic cancer after shedding from pancreatic cells [42,43]. CA 19-9 is also

released into the peripheral blood via the lymphatic system through the disruption of the cell membrane. This may be induced by necrosis or apoptosis resulting from therapy. Necrosis is usually rapid, [44] requiring only hours or a few days until the membrane is disrupted, and all contents have left the cell. The release of CA 19-9 mucin carrier complexes into the blood depends on the speed of lymphatic flow⁴⁵ and is estimated to require 1 or 2 days. Finally, the decomposition of CA 19-9 takes place via hepatic clearance and biliary secretion [19,20].

The time for total elimination of CA 19-9 due to hepatic function has not yet been published, but it can be estimated from the results of complete surgery in biliopancreatic malignancies. Consequently, concentration normalization is reached within 2-4 weeks [46]. From this, we can estimate that within 3 weeks, the patient's concentration of CA 19-9 dropped to 2.6%, 8.8%, and 16.2% with assumed biological half-lives of 4, 6, and 8 days, respectively.

The biological half-life of residual CA 19-9 in consecutive blood samples is considered to have the greatest ability to distort test results. Thus, the MLs of CA 19-9 that do not account for remnant concentrations do not represent reliable results if they are contaminated with the waste of not-yet decayed glycoproteins. One study showed apparent CA 19-9 half-lives of 9, 16, 88, and 89 days [47]. The authors, however, made a calculation in a system that received consecutive CA 19-9 from the tumor. They calculated the time until half of the CA 19-9 concentration could be detected within the serial sampling. Throughout this process, the biological half-life of CA 19-9 in serum was affected, and their claim that the half-lives were 9, 16, 88, and 89 days [47] must be interpreted as being "based on a misconception."

No consensus has yet been reached regarding the test frequency or magnitude or the kinetics of change that are likely to be significant, and over what period such a change must be maintained to be significant [15,22]. This is due to limited knowledge on the half-life of CA 19-9, among other reasons [15].

Our approach is limited to tumor markers with half-lives >4 days. Some authors propose that blood samples for CA 19-9 should be drawn in intervals of 2 or 3 weeks [12,32]. In this case, the sample frequency is in tight control at the scale of the half-life of biological decay where the decay of CA 19-9 must be considered. Tumor markers with short half-lives of a few hours, such as CYFRA, are irrelevant in the presented case.

In the presented case, surveillance CT and MRI showed a mixed response in the middle and regression at the end of chemotherapy. Per other studies on the kinetics of tumor markers [10,18] and changes in CA 19-9 serum levels, the present study provides a technique to find an improved lead time preceding the findings of CT and MRI scans by several months. This improvement is important for therapy planning as it serves as a prognostic factor to predict treatment efficacy and the risk of relapse or progression earlier than imaging results. Nevertheless, with respect to its ability to detect and stage pancreatic cancer, we support the recommendations of official guidelines to perform CT and MRI for evaluating the outcome of therapy [14]. Contrast-Enhanced Computed Tomography (CECT) is regarded as the standard diagnostic method for pancreatic cancer owing to its effectiveness and availability. However, CECT and Contrast-Enhanced Magnetic Resonance (CEMR) are restricted to morphological imaging of tissues. Imaging by 18F-fluorodeoxy-

glucose (18F-FDG) Positron Emission Tomography (PET) and CT provides direct additional metabolic and morphological information (PET/CT), which improves the diagnostic efficacy.

Huang et al. [48] retrospectively evaluated a relatively large group of cases with suspected pancreatic lesions examined by PET/CT, CECT, CEMR, and CA 19-9. They compared not only the independent diagnostic value of 18F-FDG PET/CT, CA 19-9, CECT, and CEMR imaging but also the diagnostic efficacy of different combined tests. Their results indicate that 18F-FDG PET/CT performs better than the other three tests in the diagnosis of pancreatic lesions, especially in terms of specificity and accuracy. Moreover, the joint application of PET/CT with other methods could enhance diagnostic efficiency. Determination of CA 19-9 levels, a more convenient and cheaper blood examination, could significantly improve diagnostic efficiency when combined with imaging modalities, particularly PET/CT [48]. Although the abovementioned imaging methods refer directly to the investigated tissue, CA 19-9 serum determinations refer to the indirectly obtained tumor-induced metabolic information by the detection of CA 19-9 in the serum. This is a remarkably different approach, including an additional complex biological step: the biomarker migrates through the lymphatic route to the blood vessels after being released from the tumor. Thereafter, the biomarker remains in the blood vessels according to its biological half-life. This can lead to an accumulation of remnant biomarker in the blood, which is determined in a conventional test, together with newly produced biomarker coming from the tumor site. Conventional biomarker determinations during follow-up do not consider this, and accordingly, such measurements might be less specific for changes in the status of the tumor vitality during treatment. The elimination method illustrated in this manuscript eliminates this disadvantage. The aim of this study was to present the idea of calculating only the newly produced tumor marker levels achieved by a novel method of patient follow-up. As the data are mainly descriptive and limited to a calculated and constructed model for sequentially taken blood samples from a single case report, confirmation using a large cohort and other biomarkers is warranted. When the accuracy of this method is confirmed, the present guidelines should be revised.

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